

### **REMARKS**

Applicant respectfully requests reconsideration. Claims 15 and 19 were previously pending in this application. Claims 15 and 19 are amended herein. No claim is canceled. As a result, claims 15 and 19 are still pending for examination with claim 15 being an independent claim. No new matter has been added.

#### ***Double Patenting***

Claims 15 and 19 stand provisionally rejected on the ground of nonstatutory double patenting over claims 1-20 of copending Application No. 10/472,621. Since the conflicting claims have not been allowed, Applicant respectfully requests that this provisional double patenting rejection be held in abeyance until such time as one or more claims of the co-pending application are found allowable.

#### ***Rejection Under 35 U.S.C. § 103***

Claims 15 and 19 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grimble et al. as evidenced by Grimble II.

Applicant respectfully disagrees and contends that the cited references do not render the instant claims obvious. The cited references merely teach that riboflavin, among other vitamins, is an important nutrient that is necessary in maintaining a general balance of the body's immune system. As outlined below, the cited references do not teach or suggest that riboflavin *per se* would be effective in preventing hypercytokinemia.

Indeed, the cited references indicate that many possible nutrients may have the property Applicant discovered for riboflavin sodium phosphate, but they provide no suggestion that, of all the nutrients, riboflavin sodium phosphate would have that property. This is a textbook example of an obvious-to-try rationale. Even after KSR, obvious-to-try is not enough to sustain an obviousness rejection. A reasonable expectation of success is still required. MPEP §2143 E.

If there were a small number of technical solutions, the requisite expectation of success likely existed. Id. In contrast, if there were numerous possible choices, and the art provided no guidance as to which should be chosen, there was no reasonable expectation of success, and the

obvious-to-try invention is not obvious. The Federal Circuit made this crystal clear earlier this year in In re Kubin, 561 F3d 1351 (Fed. Cir. 2009).

In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.

Applicant respectfully submits that is what the Examiner has done here, rely on hindsight to find the reasonable expectation of success required for an obvious-to-try invention to be obvious. Because there was no teaching or suggestion to vary ribovlavin sodium phosphate among the myriad nutrients Grimble suggested might influence immune function, the rejection should be withdrawn.

As noted by the Examiner, part of the balance of the immune system involves antioxidant defenses, which involve glutathione function. The Examiner asserted in the Office Action (page 5) that nutrient intake, prior to infection will influence the extent of endogenous nutrient provision. As the Examiner recognized, the cited references merely teach that the immune response to a trauma such as an infection is *influenced* by the general status of the host's nutrient levels (e.g., how well-nourished the host is). Indeed, some of the studies that are mentioned in the cited references appear to refer to situations where a host is unable to respond adequately to an infection when the host had been deprived of important nutrients such as vitamins. Therefore, Applicant submits that the cited references describe scenarios that are distinct from the instantly claimed methods.

In fact, the cited references indicate that the extent of immune responses, e.g., antioxidant defenses, is *influenced by a number of factors* and that “[t]he interaction between the response of the immune system to pathogens and inflammatory agents, and antioxidative vitamins is complex” (Conclusions, page 317 of Grimble). Specifically as to “effects of riboflavin on immune function,” the author states that while “[r]iboflavin is an important cofactor in glutathione metabolism...” (page 317), “*whether this role is responsible for the influence of the vitamin on immune function is unclear*” (page 317). However, the Office seems to equate “an important nutrient” with “sufficient to treat” medical conditions such as sepsis *when administered as a sole component*. Thus, the interpretation set forth in the Office Action does not appear to be consistent with the actual

teachings of the cited articles. Grimbale does not suggest that administration of riboflavin *per se* would be effective in preventing hypercytokinemia.

In addition, the Office has focused on the function of glutathione and the role of riboflavin as a cofactor for glutathione reductase in maintaining the homeostasis of antioxidants, which presumably in turn mediates cytokine regulation. It should be noted that, as mentioned above, Dr. Grimbale himself stated in his review article that *it was “unclear” whether the role of riboflavin as a cofactor in glutathione metabolism is responsible for the influence of the vitamin on immune function*. While the observed effect of riboflavin on the inhibition of hypercytokinemia conceivably be partially mediated via glutathione, this is merely speculation. In other words, the rejection set forth in the Office Action appears to be largely based on the Office’s speculation on the mechanism involving glutathione – a speculation the primary reference refused to make.

In the previous Office Action, the Examiner also cited Grimbale II and alleged that “where there is a deficiency i[n] riboflavin, endogenous nutrient provision provided by glutathione will lack, thereby creating a heightened immune/inflammatory response that wields the over- or hyper-production of cytokines.” It was maintained in the present Office Action that it *logically flows* that the presence of riboflavin has *an inverse relationship* with cytokine production.

Applicant respectfully contends that this is an hindsight-driven view of the regulation of cytokines. Contrary to the Office’s assertion, changes in cytokine production/concentrations are *not* necessarily correlated with riboflavin levels. It is well known in the art that patients with a riboflavin deficiency do not necessarily result in hypercytokinemia. For example, it has been well known to the person skilled in the art that stomatitis (oral inflammation), which is a type of disease associated with vitamin B2 deficiency, does not induce hypercytokinemia. Thus, the assertion that “the presence of riboflavin has an inverse relationship with cytokine production” lacks evidence.

If this is a fact within the Examiner’s personal knowledge, Applicant respectfully requests that the Examiner provide a declaration to submit that knowledge into the record so that Applicant can respond to it. See 37 C.F.R § 1.104(d)(2) (“When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of

such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.”).

Furthermore, Grimble teaches that both “vitamin B6 *and* riboflavin participate in the maintenance of glutathione status” (See *Summary* on page 312, left column). Based on this teaching, one of ordinary skill in the art would not have expected that administering in excess only one of these two vitamins would result in an enhanced immune response. For the Office’s argument to prevail, administering vitamin B6 should also induce similar effects on cytokine inhibition as riboflavin. However, there is no evidence suggesting that vitamin B6 has any effect on cytokine inhibition.

Finally, Applicant notes that the Examiner disagreed with Dr. Kodama’s (an inventor) conclusion in the Declaration that vitamin B2 had no effect on glutathione levels. The Examiner is correct that the reported levels for rats and mice (reported as the mean of 2 data) increased and decreased, respectively, after LPS and vitamin B2 administration. Those changes, however, are negligible. Moreover, Applicants are considering running this experiment with more subjects to obtain further data demonstrating the lack of a statistically significant change.

In view of the foregoing, Applicant respectfully submits that nothing in the cited references, either alone or in combination, teaches or suggests the instant invention and that the instant claims are not rendered obvious under § 103 in view of the Grimble references. Accordingly, it is respectfully requested that the rejection made under this section be reconsidered and withdrawn.

Based on the foregoing, Applicant believes that the instant claims are in an allowable condition. A favorable response is earnestly solicited.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. T0509.70011US00.

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Respectfully submitted,

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